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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/244,130	02/04/1999	BERNARD DUJON	3495.0111-10	3378

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1633	19

DATE MAILED: 12/31/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/244,130	DUJON ET AL.	
	Examiner	Art Unit	
	Sumesh kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's arguments filed on 10/10/01 and Dr. Choulika's declaration have been fully considered but they are not persuasive, for the reasons of record as set forth in the earlier office action (Paper No.15, 04/11/01).

Claims 48-93 are pending and are examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The references cited herein are of record in a prior Office action.

Double Patenting

Claims 53-57 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15, 28, 29, 30, 32 of co-pending Application No.08/643732 for the same reasons of record as set forth in the official action mailed on 4/11/01. Since this is a provisional rejection the applicant request that the rejection be held in abeyance (response: page 1, ¶3).

Claim Rejections - 35 USC § 112

Claims 48-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons of record as set forth in the official action mailed on 4/11/01.

The applicant argues that it does not matter how applicants convey the invention to one skill in the art. The applicant further argues that in instant case the applicant need not to describe the phenotype of applicant's mice and the genotype of the mice alone is a sufficient description (response: page 2, ¶2). The applicant further argues that mere presence of Group-I endonuclease recognition site is all that is required of applicant's transgenic mice comprising a Group-I endonuclease recognition site (response: page 2, ¶3). The applicant further argues that office has not given any reason why the listed endonucleases site are not representative of the claimed endonucleases (response: page 3, ¶3). The applicant further argues that there can be no doubt that applicant' s had possession of mice comprising any and all Group-I endonuclease recognition sites (response: page 4, ¶1). The applicant further argues that the phenotype of applicant's mice is predictable and no undue amount of experimentation would be required to practice the invention as claimed (response: page 5, ¶2).

Dr. Choulika's declaration disclosed that D3 cells were infected with p2MLOP014 retroviral vector that encodes a I-Sce-I site. The transfected D3 cells were injected into blastocel of the mouse blastocyst. The blasocytes were then injected into DBA2 foster mother mice which resulted in three chimeric offspring wherein the phynotypic expression ranges from 50%-85% (declaration page 2, para 7).

However, this is not found persuasive because the invention as claimed is drawn to a transgenic mice encoding Group I interon encoded endonuclease and Group I intron encoded enonuclease recognition sites. Furthermore, the invention as claimed encompasses a method of generating and culturing transgenic cells obtained from the transgenic mice as claimed. In addition, the invention as claimed encompasses a method of activation of a specific gene in the mouse cells by cleaving a Group I intron encoded endonuclease recognition site, wherein the recognition site is inserted into a gene.

The earlier office action clearly states that, the few disclosed embodiments are not representative of the products claimed. The claims encompass transgenic mice and recombinant cells provided from the transgenic mice, comprising a nucleotide sequence encoding Group-I intron encoded i) endonucleases and ii) recognition sites. The Group-I intron encoded endonucleases encompass any and all endonucleases encompassed by Class I, II, III, IV, and V I-endonucleases, wherein the Class I I-endonucleases encompass I-SceI, I-SceIV, I-CsmI and PanI endonucleases. It should be noted that the invention as claimed encompass **transgenic mice** encoding any and all Group-I intron encoded endonucleases and recognition sites and NOT the nucleic acid encoding the Group-I intron encoded endonucleases and recognition sites. At best the specification only discloses **a transgenic yeast or transformed/transfected mouse cell lines (NIH3T3, PCC7-s).** Dr. Choulika's declaration even fails to disclose a single transgenic mouse that encodes that encodes a I-Sce-I site. At best the decleration disclosed chimeric offspring wherein the phynotypic expression ranges from 50%-85%. Therefore applicant fails to disclose a single transgenic mouse encoding the Group-I intron encoded endonucleases (including I-SceI). The transgenic yeast cells, transformed mouse cell lines and/or chimeric offspring, neither represents nor predicts the phenotypic characteristic of transgenic mouse as claimed. Furthermore, disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L. P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000). Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of a transgenic mouse and/or recombinant cells (as claimed) at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed invention.

Claims 48-93 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or use** the invention for the same reasons of record as set forth in the official action mailed on 4/11/01.

The applicant arguments and Dr. Choulika's declaration are summarized in the section above.

The applicant arguments and Dr. Choulika's declaration are found unpresuasive because to exercise the invention as claimed it is not routine in the art to make and test transgenic mice that encodes any and all Group I intron encoded **endonucleases** and Group I intron encoded **enonuclease recognition sites**. The invention as claimed would certainly require extensive and undue amount of experimentation to make transgenic mice expressing any and all Group I intron encoded endonucleases and Group I intron encoded enonuclease recognition sites. Therefore, the applicants argument alone cannot take place of evidence lacking in the record (*see In re Scarbrough 182 USPQ, (CCPA) 1979*).

The earlier office action clearly states that the state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425). The transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals (Wall RJ Theriogenology 45:57-68, 1996). Furthermore, the lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the

expression of a transgene (Wall, page 61-62). The cis acting elements of one species may interact with different transactivating factors in other species. For example, the introduction of human growth hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs. (Pursel VG et al J. Reprod Fert. Sup 40: 235-245 1990, see page 235, para.1).

Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, col.1, para. 3-4, page 548, col.2 para.2). In addition, the phenotype of targeted mutations by a homologous recombination have not always been as predicted because the homologous recombination is a rare event which requires numerous step that often fails. The embryonic stem (ES) cells are very sensitive to culture conditions and have natural tendency to differentiate, giving rise to unstable genome. The homologous recombination is a rare event in ES cells and the injection of ES in the blastocyte is highly unpredictable (Viville, in Transgenic Animals, Houdebine (eds), Harwood academic publishers, France. pp307-321, 1997).

At best the specification teaches insertion of I-Sce-I site via homologous recombination in mouse NIH3T3 fibroblast and mouse PCC7-s multipotent cell lines using viral vectors (page 64, para.3, page 67, table-1). The specification only exemplified the retroviral infection of a mouse PCC7-s multipotent cell line using viral vectors but fails to disclose that implantation of any selected clone lead to the making of a trasgenic mouse (page 64, para.3, page 67, table-1). Furthermore, the specification teaches genetic recombination, especially the homologous recombination in the making of transgenic yeast (page 3, para.1-2, example 1, 2 and 3). Based upon these results the specification merely speculated that "the method can also be used with transgenic animals" (page 85 para.1, para.3). Similarly, Dr. Choulika's declaration fails to

disclose a single transgenic mouse that encodes that encodes the I-Sce-I site. At best the declaration only teaches chimeric offspring wherein the phynotypic expression ranges from 50%-85%. Therefore applicant even fails to disclose a single transgenic mouse encoding the I-SceI recognition site or I-Sce-I endonuclease.

The scope of instant claims encompass a transgenic mouse encoding any and all Group-I intron encoded endonucleases (The Group-I intron encoded endonucleases encompass any and all endonucleases encompassed by Class I, II, III, IV, and V I-endonucleases, wherein the Class I I-endonucleases encompass I-SceI, I-SceIV, I-CsmI and PanI endonucleases). The scope of instant claims also encompass a method for activation of any and all genes in a mouse cell by cleaving any Group I intron encoded endonuclease recognition site wherein the cleavage promotes the activation of expression of the gene by homologous recombination. The specification and the Dr. Choulika's declaration even fails to disclose a single transgenic mouse comprising a nucleotide sequence encoding I-SceI recognition site and/or endonuclease, wherein the transgene (as claimed) is introduced by homologous or non-homologous recombination. In addition, the methods of generating, culturing the transgenic cells, are not enabled because the method (as claimed) requires the use of cells obtained from a transgenic mouse.

Furthermore, considering the unpredictability in the transgenic art (*supra*) and the guidance provided in the specification it is unclear how one skill in the art would use D3 embryonic stem cells without excessive and undue amount of experimentation to generate variety of transgenic mice encoding any and all Group-I intron encoded endonuclease sites or endonucleases. Viville's clearly states that although D3 embryonic stem cell line is an excellent embryonic stem cell line, creating a transgenic mice is not as easy task because technique is very long and there are many steps that often fails. To make and test is not the standard for enablement. The phenotype of a tansgenic animal is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The applicant fails to disclose a single working example that encompasses the invention as claimed. It is unclear how one skill in the art would exercise the invention as claimed when the phenotype of a transgenic mouse (as required) is not known. Furthermore, considering the unpredictability in the

transgenic art transgenic yeast or transfection of mouse cell lines in vitro does not recapitulate the complexities involved in the making of transgenic animals.

In addition, the scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the genus of transgenic mice encoding any and all Group-I intron endonuclease sites and enddonucleases, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Thus, in view of lack of specific guidance in the specification, the skilled artesian at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. Although, one skilled in the art would have been able to make the required genetic constructs encoding any and all Group-I intron encoded endonuclease sites, it would have required excessive and undue experimentation to make transgenic mice encoding any and all Group-I intron encoded endonuclease sites, without a predictable degree of success because the specification only provide guidance to make a transgenic yeast or transfected mouse cells encoding I-SceI site.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and **A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED** to facilitate further examination.

SUMESH KAUSHAL
Patent examiner

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER